UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,798	11/12/2003	Carlo Croce	3589.1008-002	8331

21005 7590 12/31/2007

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
12/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,798	CROCE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17,52 and 75-104* is/are pending in the application.

4a) Of the above claim(s) *16,17,75-88,95 and 96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52, 89-94 and 97-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amended claims 16-17, 52 and new claims 75-104 are pending in the present application.

Applicant's election of intravenous administration as a species of parenteral administration in the reply filed on 10/03/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Previously, Applicant's election with traverse of Group XI (claims 16-17, 40-49 and 52), **drawn to a method of treating an miR15 mediated cancer in a subject in need of such treatment using autologous cells transfected with a nucleic acid comprising sequence encoding an effective amount of an miR15 gene product**, in the reply filed on 10/6/06 is acknowledged. **Applicants also elected previously the following species: (a) prostate cancer cells as the species of transfected cells; (b) cytomegalovirus promoter as the species of promoter; and (c) an adeno-associated virus vector as the species of recombinant viral vector**.

Accordingly, claims 16-17, 75-88 and 95-96 were withdrawn from further consideration because they are directed to non-elected species.

Therefore, claims 52, 89-94, 97-104 are examined on the merits herein **with the previously elected species**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 16-17, 75-88 and 95-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***This is modified rejection necessitated by Applicant's amendment.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

1. The breadth of the claims

With respect to the elected invention, the instant claims are directed to a method of treating a prostate cancer in any subject comprising the step of administering into the subject at any site (e.g., by intravenous administration) any cell derived from any source, **not necessarily limited to an autologous cell** (present in originally filed claims 16-17, 40-49 and 52 in the elected invention), as long as the cell was transfected

with any nucleic acid (including one comprising the elected recombinant adeno-associated virus vector containing the elected cytomegalovirus promoter) comprising a nucleotide sequence encoding a miR15 gene product (transfected prostate cancer cells as the elected species).

2. The state of the prior art and the unpredictability of the prior art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the instant application (11/13/2002), gene therapy was and continues to be immature and unpredictable, particularly for attaining any therapeutic effects. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression, immune manipulation, is needed to make **gene therapy a reality**. Dang et al. also pointed out several factors limiting an effective human gene therapy, including, sub-optimal vectors, the lack of a stable *in vivo* gene expression, and most importantly **the lack of an efficient gene delivery to targeted cells or tissues** (last paragraph, page 474). Romano et al. (Stem Cells 18:19-39, 2000) state "The potential therapeutic applications of gene transfer technology are enormous. However, **the effectiveness of gene therapy programs is still questioned**", and "[d]espite the latest significant achievements reported in vector design, **it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame**" (see abstract, col. 2). Even in 2005, Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005) still state "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological

disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but **it has yet to deliver its promised potential**", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, **gene therapy will be added to our medicinal armada** and the ever-expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph).

Additionally, at about the effective filing date of the present application (11/13/02), little was known on the function of microRNAs, including miR15, let alone for using these microRNA in the form of *ex vivo* gene therapy to attain a desired therapeutic effect such as treating or inhibiting proliferation of any miR15 mediated cancer such as prostate cancer using any cell derived from any source that has been transfected with a nucleic acid encoding a miR15 gene product, including the elected transfected prostate cancer cells from the subject in need of treatment. Lagos-Quintana et al. (Science 294 :853-858, 2001; IDS) state "**The challenge for the future is to define the function and the potential targets of these novel miRNAs** by using bioinformatics as well as genetics and to establish a complete catalog of time-and tissue-specific distribution of the already identified and yet to be uncovered miRNAs" (page 857, top of col. 2).

3. The amount of direction or guidance provided

Apart from the exemplification showing that the miR15 gene is located at 13q14 within a 30-kb region of loss in chronic lymphocytic leukemia (CLL), and the gene is deleted or down-regulated in the majority of CLL cases, the instant specification fails to provide sufficient guidance, including any relevant examples, for a skilled artisan on

how to attain any therapeutic effect (for this instance inhibition of MiR15-mediated cancer cell proliferation in a patient, by implanting at any site in the patient autologous prostate cancer cells transfected with a recombinant adeno-associated virus vector expressing an effective amount of an miR15 gene product (the elected species), let alone for any cell derived from any source as long as it is transfected with a nucleic acid encoding a miR15 gene product. **Firstly, there is no evidence of record or in the prior art at the effective filing date of the present application indicating or suggesting that any cancer cell, including prostate cancer cells, is able to target or home in to any cancer site from any administered site in a patient. Secondly, the miR15 gene product is an intracellular product.** Then how does an effective amount of the miR15 gene product expressed in implanted, genetically modified cells or prostate cancer cells exert their effect on other cancer cells in the patient that are not genetically modified, particularly for cancer cells that are not at the same site as the delivery site, to attain the desired therapeutic effect? There is no evidence of record suggesting or indicating that any recombinant miR15 gene product is diffused from prostate cells or cells transfected *ex vivo*, and it is being transported into other non-transfected cancer cells in the patient at an effective concentration to yield the desired therapeutic effect. **Thirdly, available recombinant adeno-associated viral vectors at the effective filing date of the present application are replication defective. Then, how can the implanted autologous genetically modified prostate cancer cells effectively deliver an effective amount of miR15 gene product to other cancer cells present in the patient to yield the desired therapeutic effect. Fourthly, with**

respect to an administered transfected cell derived from any source (e.g., xenogeneic, allogeneic as well as autologous cells), the instant specification also fails to provide sufficient guidance for a skilled artisan on how to overcome the vigorous host rejection reactions against non-autologous transfected cells, such that these transfected cells would persist in the treated subject for a sufficient period of time to express an effective amount of a miR15 gene product, and somehow this miR15 gene product can exert its activity in non-transfected prostate cancer cells to yield the desired therapeutic effects, particularly the transfected cells were administered through an intravenous delivery route.

Accordingly, in light of the state of the gene therapy art, particularly little was known on the function of microRNAs (e.g., miR15) as discussed above, coupled with the lack of sufficient guidance provided by the present disclosure regarding to the aforementioned issues, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Response to Amendment

Applicant's arguments related in part to the above rejection in the Amendment filed on 5/18/07 (pages 10-11) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the enablement rejection should be withdrawn in light of the presently amended claims. Applicants further cited various paragraphs of

the present disclosure that teach the vector, cells to be transfected, route of delivery and how to treat a prostate cancer in a subject.

Firstly, it is noted that the presently amended claims have the same fundamental enablement issues as those of previously presented claims 16-17, 40-49 and 52. Please see the above modified rejection with the enablement rejection in the Office Action mailed on 11/14/2006 (pages 4-8).

Secondly, just describing how to treat a prostate cancer in a subject for a method as claimed, this description of the method by itself is not sufficient or necessary that the claimed method is enabled. Please see the detailed analysis of the Wands factors and issues set forth in the above rejection why the presently claimed invention is not enabled.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D.
PRIMARY EXAMINER